Review

Noradrenergic and serotonergic mechanisms in the neurobiology of posttraumatic stress disorder and resilience

John H. Krystal[a], Alexander Neumeister[a,b,*]

[a]Department of Psychiatry, Yale University School of Medicine, New Haven, CT, USA
[b]Molecular Imaging Program, Clinical Neurosciences Division, National Center for PTSD, VA Connecticut Healthcare System, West Haven, CT, USA

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ABSTRACT

Posttraumatic stress disorder (PTSD) is characterized mainly by symptoms of re-experiencing, avoidance and hyperarousal as a consequence of catastrophic and traumatic events that are distinguished from ordinary stressful life events. Although extensive research has already been done, the etiology of PTSD remains unclear. Research on the impact of trauma on neurobiological systems can be expected to inform the development of treatments that are directed specifically to symptoms of PTSD. During the past 25 years there has been a dramatic increase in the knowledge about noradrenergic and serotonergic mechanisms in stress response, PTSD and more recently in resilience and this knowledge has justified the use of antidepressants with monoaminergic mechanisms of action for patients with PTSD. Nevertheless, available treatments of PTSD are only to some extent effective and enhanced understanding of the neurobiology of PTSD may lead to the development of improved treatments for these patients. In the present review, we aim to close existing gaps between basic research in psychopathology, neurobiology and treatment development with the ultimate goal to translate basic research into clinically relevant findings which may directly benefit patients with PTSD.

Contents

* Corresponding author. 950 Campbell Avenue West Haven, Connecticut 06516, USA. Fax: +1 203 937 3481.
  E-mail address: alexander.neumeister@yale.edu (A. Neumeister).

1. Introduction

1.1. The concept of PTSD and resilience

The definition of posttraumatic stress disorder (PTSD) in DSM-IV (American Psychiatric Association, 1994) links a specific syndrome characterized mainly by symptoms of re-experiencing, avoidance and hyperarousal with catastrophic and traumatic events that are distinguished from ordinary stressful life events. Epidemiological surveys in the United States have documented that the probability of developing PTSD following traumatic exposure is approximately 10% (Breslau et al., 1998; Kessler et al., 1995); women are more likely than men to develop PTSD once trauma occurs (Breslau et al., 1999; Norris, 1992; Stein et al., 1997; Stein et al., 2000). The increased morbidity (Hoge et al., 2007; Kubzansky et al., 2007), disability (Schnurr et al., 2006; Zatzick et al., 1997) and mortality (Boscarino, 2006) associated with PTSD call for increased efforts to develop more informative models for testing pathophysiologic and treatment hypotheses.

To date, there exists an important gap in trauma research because whereas available research has made important contributions to understand risk factors for negative mental health consequences of traumatic stress exposure, the identification of characteristics associated with resilience to the impact of traumatic stress exposure could inform studies of preventive and treatment procedures for people with or at risk of trauma exposure (Rutter, 1985). Resilience, in contrast to recovery from symptomatic PTSD, is defined as the absence of psychopathology by DSM-IV criteria in adults who were exposed to extreme life stressors (Bonanno et al., 2007; DuMont et al., 2007; Tiet et al., 1998). A relatively large body of research has focused on the identification of psychosocial factors associated with the capability of trauma-exposed individuals to successfully adapt to extreme stress exposure. These studies have shown that lower lifetime trauma load (Breslau et al., 2008), male gender (Brewin et al., 2000), the use of adaptive coping strategies, e.g. emotional expression or the ability to elicit social support, optimism, cognitive flexibility, mastery, religion, and purpose in life, and the lower use of avoidant coping strategies, e.g. denial are associated with resilience (Alim et al., 2008; Yehuda et al., 2006b). Comparatively few studies have examined neurobiological mechanisms that confer resilience and thereby allow successful adaptation to extreme stress exposure without developing psychopathology. From a neurobiological perspective, preclinical and clinical studies have provided strong evidence that neuropeptide Y, and the monoamines serotonin (5-HT) and norepinephrine (NE) play an important role in models of resilience.

Given that current prevention and treatment strategies for PTSD are non-optimal, additional research is needed to investigate basic mechanisms underlying the adaptive and maladaptive responses to severe stress in order to decrease the devastating impact of these disorders on public health. PTSD is increasingly understood to involve central neurotransmitter imbalances and neuroanatomical disruptions (Fig. 1.), along with potential dysregulation of immune, autonomic, endocrine function, and cardiovascular function. In this paper emphasis is placed on recent advances in PTSD research, and discussion on future directions that might catalyze discovery of innovative treatments.

1.2. Current treatment challenges

There have been significant advances in the pharmacotherapy of patients with PTSD, and certain medications, e.g. selective serotonin reuptake inhibitors are considered first-line treatment for adult PTSD. Nevertheless, residual symptoms after treatment are more the rule than the exception and there is concern that further research will conclude that chronicity leads to progressive treatment resistance. This has led to a shift with new emphasis on treating both acute and residual symptoms of PTSD more aggressively, with a close eye being kept on functional impairment. About 40% of patients with PTSD do not meet typical response criteria to an initial course of antidepressants, and furthermore the majority of patients are not symptom free with monotherapy (Stein et al., 2006). In fact, remission rates for sertraline, the only FDA approved antidepressant to treat PTSD are about 25% (Davidson, 2004) and therefore there is a need for additional research about how to enhance effectiveness of the existing treatment strategies for PTSD (Dieperink et al., 2005). Also, there exists a paucity of long-term trials, data on treatment effectiveness in wider clinical practice, and data on treatment-resistant patients.

This highlights the importance of defining novel targets for treatment of people with PTSD, an area of intensive research efforts around the world. Consequently, this report links the endophenotype of PTSD with the neurobiology of the disorder
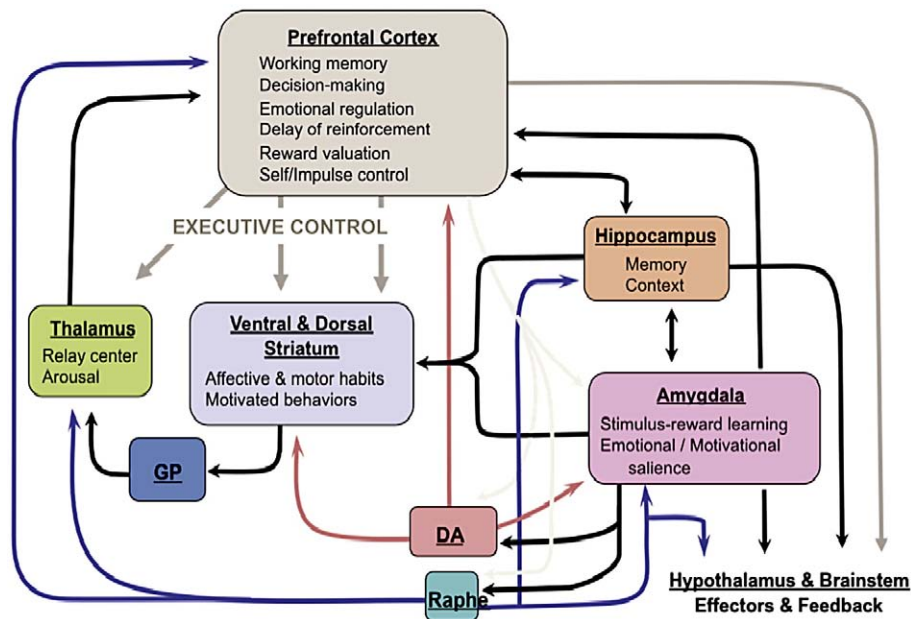
Fig. 1 – Acute and repeated stressors disrupt frontal-cortical control over limbic-striatal circuits which constitute the brain stress circuit, increase mesolimbic dopaminergic transmission and increase prefrontal cortex (PFC) norepinephrine (NE) and serotonin (5-HT) transmission. The prevailing neurocircuitry model of PTSD which has been developed from theoretical considerations, research in animals and expanded to human imaging studies emphasizes the role of the amygdala, as well as its interactions with the ventral/medial prefrontal cortex (vmPFC), hippocampus and anterior cingulate cortex. The model hypothesizes hyperresponsivity of the amygdala to threat-related stimuli and deficient ventromedial PFC function but also evidence for generalized hypervigilance in PTSD.

as well as mechanisms of resilience with a particular emphasis on monoaminergic mechanisms to help move translational research forward with the goal to identify novel targets for drug development.

2. Neurochemistry of PTSD: the role of norepinephrine

Clinical evidence suggests an important role for NE in PTSD. Given the prominence of hyperadrenergic symptoms in PTSD (e.g. hyperarousal, reexperiencing, anxiety, tachycardia, increased diastolic blood pressure, diaphoresis), which characterize patients with PTSD, the noradrenergic/locus coeruleus (LC) system and its varied pathways have been the focus of many neurobiological investigations in PTSD over the past 25 years. There is now considerable evidence that abnormal regulation of brain NE systems is observed in patients with PTSD. In particular, NE activity in the cell bodies of the LC and projections to the amygdala, hippocampus and prefrontal cortex (PFC) are thought to be important in fear and stress responses (O'Donnell et al., 2004; Shin et al., 2006). Pharmacological challenge studies with yohimbine in humans (Bremner et al., 1997; Southwick et al., 1993; Southwick et al., 1997), animal studies (Arnsten, 1998; Arnsten et al., 1998) and neuropsychological studies in patients with PTSD (Clark et al., 2003; Galletly et al., 2001; Stein et al., 2002; Vasterling et al., 2002) provide additional evidence for the importance of NE in PTSD.

2.1. Norepinephrine transporter

Chronic depolarization of sympathetic neurons induces NE transporter (NET) expression through increasing catecholamines (Habecker et al., 2006). Pre-clinical studies show that the endogenous substrates dopamine and NE stimulate NET expression in the central and peripheral nervous systems (Arnsten et al., 1999; Arnsten and Li, 2005; Avery et al., 2000; Lee et al., 1983; Li et al., 1999; Li et al., 1994; Mao et al., 1999; Swann et al., 1985; Weinshenker et al., 2002) and may serve as a model of NET regulation during pathophysiology. This is important because deficits in NE transmission are implicated in psychiatric disorders, and antidepressant drugs that block the NET have shown efficacy in stress-associated mood (Cipriani et al., 2009) and anxiety disorders (Stahl et al., 2005). In animal studies it was shown that most PFC NE axons have an unrecognized, latent capacity to enhance the synthesis and recovery of transmitter which could be an important mechanism in the capacity of adapting to stress which could have been vanished in individuals with PTSD. Chronic exposure to stress leads to increase of plasmalemmal NET expression in the PFC suggesting that this mechanism is an attempt to maintain the normal availability and consequently normal function of dopamine and NE in the PFC (Miner et al., 2006). In the LC, however, chronic stress leads to a reduction of NET availability (Rusnak et al., 2001), which may result in exaggerated synaptic availability of NE in projection areas. Despite these convincing animal models, it is unclear to date whether these models can be

applied to humans. The availability of novel radiotracers for the NET (Ding et al., 2005) using positron emission tomography provide an opportunity to study these mechanisms in vivo. Manifestations of NET abnormalities could be important markers for identifying and subtyping patients with PTSD which could become relevant to the treatment of PTSD because NETs are high-affinity targets of antidepressant agents and NET inhibitors, e.g. desmethylimipramine, reboxetine or atomoxetine which are highly selective NET inhibitors have been used as antidepressants for many years (Cipriani et al., 2009) but their role in the treatment of PTSD is unclear yet.

2.2.   Alpha-2 adrenoreceptors

Recent transgenic experiments suggest that the alpha-2 adrenoreceptor may emerge as a target of specific interest to PTSD. Knockout of the gene for the α2a receptor increases immobility in the forced swim test and eliminates the augmentation of forced swim test activity by imipramine (Schramm et al., 2001). In contrast, other recent experiments suggest that mice lacking α2c receptors perform on the forced swim test in the *same* fashion as mice treated with antidepressants (Sallinen et al., 1999). Thus, the α2a and the α2c receptors may have complementary and *opposing* roles in the regulation of mood and anxiety (Small et al., 2000). If reducing α2c activity is to be used as an antidepressant/anxiolytic strategy it may require some method of targeting only those receptors in the CNS since it was shown recently that an α2c (Del322–325) polymorphism reduces feedback inhibition of sympathetic NE released (Neumeister et al., 2005). Recent evidence that a mutation of the α2a receptor impairs working memory could also help us understand the cognitive symptoms observed in PTSD (Franowicz et al., 2002), and drugs that specifically enhance function of the α2a receptor may be a novel way to treat symptoms of PTSD, even though unspecific α2 receptor agonists failed to show superiority over placebo in the treatment of chronic PTSD (Davis et al., 2008; Neylan et al., 2006).

2.3.   Interactive effects of norepinephrine with other neurobiologic systems

2.3.1.   Crosstalk with serotonin and dopamine
It is clear that NE transmission does not fully explain the neurobiology of PTSD and changing the set point of NE transmission cannot fully explain antidepressant action and their effects, but there is a growing body of evidence showing that plastic changes in the limbic target areas of monoamine neuron projections are important in the mechanism of action of antidepressants and therefore of relevance to the neurobiology of PTSD. It appears that the behavioral effects of NE, 5-HT, and dopamine have a considerable overlap such that augmenting levels of any one may have antidepressant effects, and increasing synaptic levels of more than a single neurotransmitter may be synergistic (Thase et al., 2001). Crosstalk between NE neurons, dopamine, and 5-HT neurons has been documented such that increased NE stimulates 5-HT and dopamine release, and 5-HT release at NE neurons reduces NE release. As another example, blockade of the

NET can reduce the uptake of dopamine in the frontal cortex since the NET has high affinity for dopamine (in fact NET has a higher affinity for dopamine than does the dopamine transporter itself), and dopamine transporters in any event are found at low levels in frontal cortex, suggesting that drugs that inhibit the NET may be capable or specifically effective in PTSD by affecting prefrontal dopamine signaling behavior (for review (Arnsten and Li, 2005)).

2.3.2.   Interactive effects with neurosteroids
Crosstalk between the catecholamine system and steroids may be another novel mechanism through which NE and epinephrine by increasing the sensitivity of glucocorticoid receptors to ligand activation could alter symptoms of PTSD (Zhu et al., 1999). Augmentation effects of catecholamines on GR signaling may thus be important in cognitive and emotional processing. The PI3-K signaling pathway activation through beta receptors appears to be responsible for this putative enhancement of glucocorticoid receptor activity and it is tempting to conjecture that antidepressants which are known to down regulate beta receptors and influence PI3-K signaling could act by glucocorticoid receptor sensitization.

2.3.3.   Interaction of norepinephrine with neuropeptide Y
Neuropeptide Y (NPY), a 36-amino acid peptide, is one of the most abundant and highly evolutionarily conserved polypeptides found in the brain. Its highest concentrations are in the LC, hypothalamus, septum, and periaqueductal grey, with moderate levels in the hippocampus, amygdala, and brainstem (Silva et al., 2005), areas, which are implicated in arousal and in the assignment of emotional valences to stimuli and memories. Of the 5 NPY receptor subtypes found in mammals (Y1–Y5), the NPY-Y1 receptor is most closely studies in stress and anxiety models (for review (Thorsell, 2008)). NPY has been shown to be involved in fear consolidation, with studies showing that administration of NPY impairs retention of traumatic memories, reduces anxiety during stressful tasks, enhanced extinction of fear-potentiated startle (Gutman et al., 2008), and the haplotype-
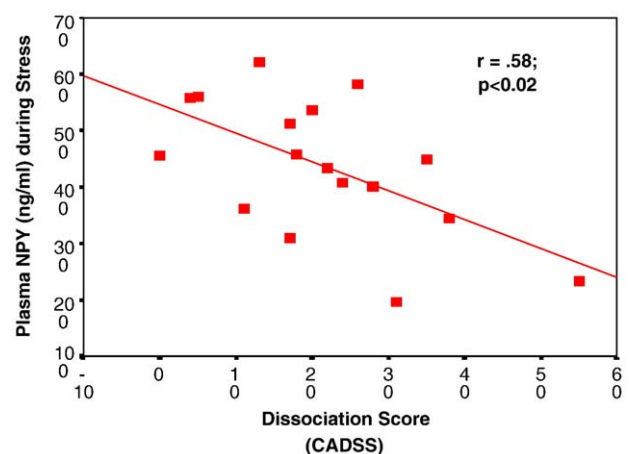

Fig. 2 – Correlation between psychologic symptoms of dissociation at baseline predict significantly less NPY release during stress in a group of N = 25 active duty U.S. Navy personnel participating in survival school training.
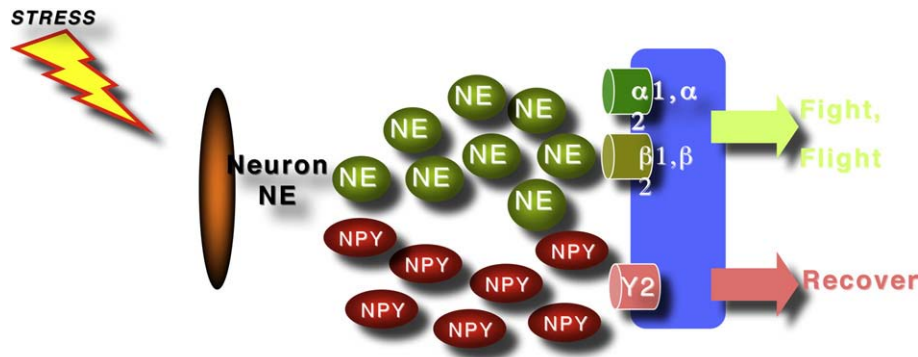
Fig. 3 – The effects of the sympathetic nervous system are mediated via release of neurotransmitters and neuropeptides from sympathetic neurons. NPY and tyrosinhydroxylase are likely to modulate NPY and/or norepinephrine (NE) release whereby NE seems to moderate the flight and fight response during stress whereas NPY contributes to dampen down the effects of NE during stress response.

driven NPY expression predicts brain responses to emotional and stress challenges (Zhou et al., 2008). NPY also mediates the response to chronic stress, by increasing expression of amygdala NPY mRNA (de Lange et al., 2008).

Human studies of NPY in people exposed to extreme stress support the idea that NPY not only confers anxiolytic activity but may also be involved in stress resilience. It was shown (Morgan et al., 2000), and subsequently replicated (Morgan et al., 2002), that Special Forces soldiers who underwent an extremely stressful training program had higher and sustained NPY levels than non-Special Forces soldiers during extreme stress, which was associated with better performance and lower stress-induced dissociation (Fig. 2). In PTSD, patients relative to non-stressed healthy controls showed lower baseline plasma NPY levels and a blunted yohimbine-induced NPY increase suggesting impaired reagibility of the system to a pharmacologic stressor (Rasmusson et al., 2000). These results were independently confirmed by another group reporting that combat-exposed veterans without PTSD had higher NPY levels than non-combat-exposed veterans, but comparable to combat-exposed veterans with PTSD (Yehuda et al., 2006a). They also reported that those veterans with past PTSD had higher plasma NPY than those without past PTSD suggesting that plasma NPY levels may represent a biologic correlate of resilience to or recovery from the adverse effects of stress exposure. These data suggest that NPY may not only play an unspecific role in the psychobiology of stress responses, but is also involved in mechanisms of resilience and PTSD (Eaton et al., 2007), and available data are consistent with the function of NPY as an anxiolytic peptide. Altogether, it can be hypothesized (Fig. 3.) that whereas NE mediates the fight and flight response to stress, NPY may have a role in dampening the impact of NE and may therefore be a system of interest for the development of novel treatment approaches in PTSD.

3. The role of serotonin

The brain 5-HT system is involved in the regulation of stress and anxiety (Chaouloff, 1993; Griebel, 1995; Harvey et al., 2004)

and several preclinical studies have reported an increase in 5-HT release, enhanced neuronal activity in the dorsal raphe nuclei, and increased 5-HT synthesis and turnover in response to stress (Chaouloff et al., 1999; Dunn, 1988). These stress-induced alterations in 5-HT activity occur in multiple brain regions, which have been implicated in the pathophysiology of PTSD, including the amygdala (Mitsushima et al., 2006), ventral striatum (Amato et al., 2006), and the PFC (Bruening et al., 2006; Gobert et al., 1998; Smith et al., 2006).

Brain 5-HT systems have been linked to the neurobiology of PTSD because the administration of m-chlorophenylpiperazine (mCPP), a 5-HT agonist, could transiently evoke symptoms of PTSD but these effects were not observed when mCPP was administered to patients with other psychiatric disorders (Charney et al., 1988; Krystal et al., 1996; Price et al., 1997). Brain 5-HT systems are also implicated in PTSD treatment. Currently, two exemplars of a single class of medications, drugs that block re-uptake of 5-HT, are the only FDA-approved treatment for PTSD. However, in the absence of knowledge about the regulation of specific 5-HT receptors in PTSD, it is difficult to directly link the efficacy of these medications to the neurobiology of the disorder. Neurons, glia, and endothelial cells possess at least 14 distinct receptors, and 5-HT is involved "in more behaviors, physiological mechanisms, and disease processes than any other brain neurotransmitter" (reviewed in (Pineyro and Blier, 1999)). Agents that enhance serotonergic activity such as the 5-HT reuptake inhibitors (SSRIs), which block the 5-HT transporter, are partially effective in PTSD (Stein et al., 2006). Serotonin, in development and adulthood has an important role in CNS neuroplasticity. Clinical and preclinical studies have thus far mostly implicated stimulation and interaction of 5-HT_{1A}, 5-HT_{1B}, and 5-HT_{2A} or 5-HT_{2C} receptors in antidepressant/anxiolytic action, but this emphasis may be in part an artifact related to the availability of selective ligands for these receptor subtypes.

3.1. The 5-HT_{1A} receptor

The 5-HT_{1A} receptor is a seven transmembrane G-protein coupled receptor found both at presynaptic locations in the raphe nucleus and at postsynaptic locations, and is critically

involved in regulating mood and anxiety levels. Postsynaptic stimulation in the hippocampus augments synaptogenesis in adult animals via a trophic factor referred to as S-100β (Whitaker-Azmitia and Azmitia, 1989; Whitaker-Azmitia et al., 1990). 5-HT$_{1A}$ receptors signal via a Gα$_i$ coupled inhibition of adenylyl cyclase and by hyperpolarization via the opening of a K+ channel. The density and mRNA expression of 5-HT$_{1A}$ receptors appear *insensitive* to reductions in 5-HT transmission associated with lesioning the raphe or administering the 5-HT depleting agent, PCPA (Frazer and Hensler, 1990; Hensler, 2002; Verge et al., 1986). Similarly, *elevations* of 5-HT transmission resulting from chronic administration of SSRI or monoamine oxidase inhibitors (MAOI) do not consistently alter 5-HT$_{1A}$ receptor density or mRNA in the cortex, hippocampus, amygdala, or hypothalamus (Carli et al., 1996; Spurlock et al., 1994; Welner et al., 1989).

The 5-HT$_{1A}$ receptor may counteract the effects of activation of the 5-HT$_{2A}$ receptor. Activation of the 5-HT$_{1A}$ receptor exerts a hyperpolarizing effect on cortical neurons whereas activation of the 5-HT$_{2A}$ receptor is depolarizing. Activation of 5-HT$_{2A}$ receptors results in glutamate release from thalamo-cortical afferents and increased levels of glutamate reduce neural, vascular, and glial trophic factors which, in combination with direct glucocorticoid effects, contribute to disruption of neurogenesis, and even neural death, in limbic and cortical brain regions (Hoebel et al., 2007). Thus, loss of neural connectivity may impede behavioral resilience to stress, giving rise to features of PTSD ("learned helplessness") and impaired learning/memory in animal models. Therefore, it is tempting to speculate that a drug designed to combine 5-HT$_{1A}$ agonism with postsynaptic 5-HT$_{2A}$ antagonism would have robust anxiolytic action.

Recent knockout experiments of the 5-HT$_{1A}$ receptor indicate that the receptor is important early in development with respect to affect-regulated behaviors. 5HT$_{1A}$ null mice have increased anxiety, but 'rescue' at a later age in conditional knockouts does not reduce anxiety if the receptor was absent at a developmentally crucial early period (Mayorga et al., 2001). Knockout of the 5HT$_{1A}$ receptor, possibly by eliminating feedback inhibitor, has the effect of reducing immobility in the tail suspension test, simulating antidepressant action. However, rather than being the result of simply increasing synaptic serotonin, challenge studies employing AMPT have implicated augmentation of catecholamine function in the antidepressant-like behavioral effects of 5-HT$_{1A}$ receptor deletions.

It was unclear, however, whether these animal models of anxiety (Bruening et al., 2006; Groenink et al., 2003a; Groenink et al., 2003b) have relevance to disease models of PTSD, and the role of the 5-HT$_{1A}$ receptor in adult PTSD was not directly studied. Data from a relatively small brain imaging study using a selective 5-HT$_{1A}$ receptor antagonist radioligand and PET did not support a direct role of this receptor subtype in PTSD (Bonne et al., 2005) (Fig. 4.), even though these studies do not exclude the possibility that 5-HT$_{1A}$ receptors play an important role in the treatment of PTSD.

3.2. The 5-HT$_{1B}$ receptor in a model of adaptive and maladaptive responses to stress

Given that epistasis among pre-synaptic components of the 5-HT transmitter system appears to be important in the 5-HT system's regulation of synaptic 5-HT levels (Stoltenberg, 2005), the 5-HT$_{1B}$ receptor is a particularly attractive candidate for further study (Clark and Neumaier, 2001). 5-HT$_{1B}$ receptor knockout (KO) studies (Groenink et al., 2003b) and the viral-mediated gene transfer approach (Clark et al., 2002) leading to 5-HT$_{1B}$ receptor overexpression support the
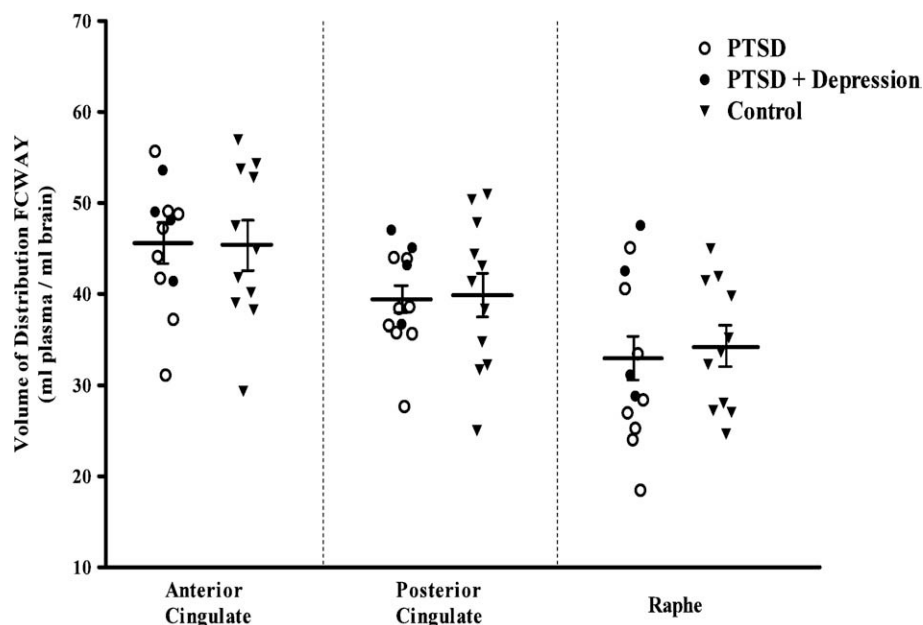
Fig. 4 – Positron emission tomography study of 5-HT$_{1A}$ receptors with the radioligand [18F]Trans-4-fluoro-N-2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl]-N-(2-pyridyl)cyclohexanecarboxamide (FCWAY), a selective 5-HT$_{1A}$ receptor antagonist ligand. No difference in receptor expression was found in PTSD or PTSD and depression vs. healthy control subjects.

concept that increased dorsal raphe 5-HT$_{1B}$ autoreceptor tone would predispose animals to increased anxiety (Clark et al., 2002) and altered stress reactivity (Neumaier et al., 2002) by reducing 5-HT availability in forebrain terminal fields. Decreased 5-HT$_{1B}$ receptor responsiveness is believed to occur in response to agonist stimulation (Janoshazi et al., 2007) and results in increased synaptic 5-HT availability (Fig. 5). We and others (Kilpatrick et al., 2007; Ursano et al., 2008) propose that increased synaptic availability of 5-HT in the amygdala (Mitsushima et al., 2006), cortical regions (Bruening et al., 2006; Smith et al., 2006), and 5-HT mediated alterations in dopamine release in the ventral striatum (Amato et al., 2006) in response to trauma is critical to avoid symptom development after trauma resulting in the PTSD phenotype and the 5-HT$_{1B}$ receptor may play a critical role in this process. It can be speculated that reductions in 5-HT$_{1B}$ receptors in cortical-striatal-limbic circuits either predict adaptive responses to stress or are a persisting feature of resilient stress responses. This hypothesis is supported by directly linking disturbances in 5-HT$_{1B}$ receptor function to the development stress-induced disorders (Sari, 2004) and also to characteristic symptoms of PTSD, i.e. anxiety, irritability and impulsivity (Clark and Neumaier, 2001). Therefore, we believe that proper 5-HT$_{1B}$ receptor function is a critical mechanism that may prevent symptom development after trauma exposure whereas compromised 5-HT1B receptor function may increase the risk to develop PTSD after trauma exposure. Because 5-HT$_{1B}$ autoreceptors positively regulate 5-HT uptake by 5-HT transporters, these coinciding proteins may provide an opportunity for synergistic effects to modulate serotonergic function. Therefore, our findings are in line with recent reports suggesting that 5-HT$_{1B}$ receptor antagonists may enhance the efficacy of selective 5-HT reuptake inhibitors (Muraki et al., 2008; Starr et al., 2007) which are typically used as first line treatments for patients with PTSD (Stein et al., 2006).

4. Conclusions

Despite the large increase in knowledge about the neurobiology of stress as well as adaptive and maladaptive responses to stress exposure resulting in the phenotype of PTSD, there is concern that there is a slow-down in the development of truly innovative novel treatments for patients with PTSD. In the area of PTSD, some of this difficulty reflects the high rate of negative and failed trials, related in part to the tremendous genetic and phenotypic heterogeneity in PTSD, and the lack of biological markers to guide drug development. Existing or novel endophenotypes that reduce the syndrome of PTSD to discrete component units and ultimately fundamental units linked to pathophysiology may help move translational research forward. Clinical and genomic approaches are needed to clinically subgroup patients more precisely. Refinement of measurement tools including imaging techniques may lead to the definition of new endpoints, and biomarkers may be developed based on dissected components of current consensus syndromes that measure disease state with accuracy and objectivity.

Acknowledgments

5HT1B receptors: PRESYNAPTIC: feedback inhibition of 5HT
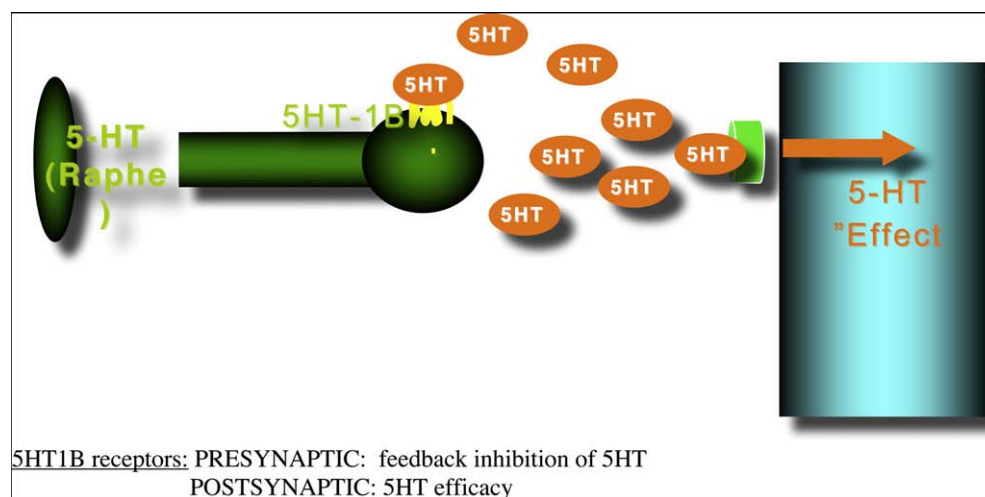POSTSYNAPTIC: 5HT efficacy

Fig. 5 – The occurrence of a traumatic event and/or chronic stress leads to increased synaptic 5-HT levels in the amygdala and cortical regions, as well as alterations in dopamine release in the ventral striatum (VST). These effects are at least partially mediated by 5-HT$_{1B}$ receptors. A PTSD-resilience model that implicates a central role for the 5-HT$_{1B}$ receptor would assume that PTSD patients, in contrast to resilient people are unable to downregulate 5-HT$_{1B}$ receptors which will lead to amygdala hyperresponsiveness because of reduced 5-HT activity which may disinhibit excitatory activity by reducing the stimulation of 5HT$_{1A}$ receptors located on pyramidal cells where they inhibit action potential formation, and of 5-HT$_3$ receptors, that are located on GABAergic interneurons where they stimulate GABA release, alterations in dopamine release in the VST and changes in ventromedial prefrontal cortex (vmPFC) function resulting in inadequate top-down governance over the amygdala by the vmPFC which is characteristic for PTSD.

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